[^{11}C]2-(2-((Dimethylamino)methyl) phenylthio)-5-(2-fluoroethyl)phenylamine [^{11}C]AFE

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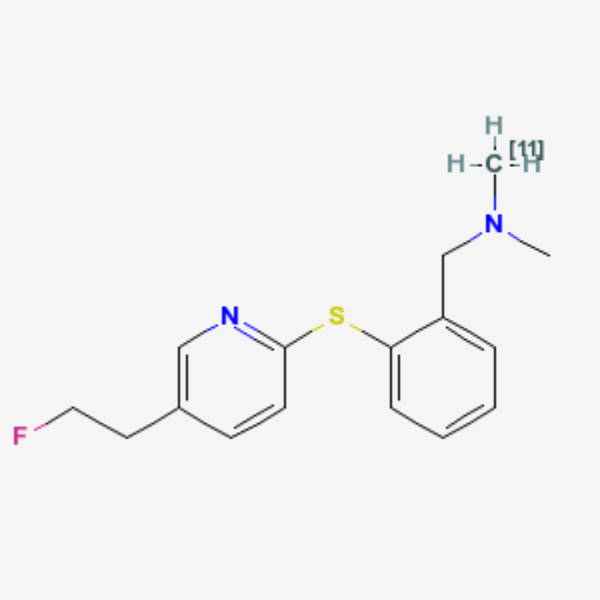
Chemical name:	[^{11}C]2-(2-((Dimethylamino) methyl)phenylthio)-5-(2-fluoroethyl)phenylamine
Abbreviated name:	[^{11}C]AFE
Synonym:	
Backbone:	Compound
Target:	Serotonin transporter (SERT)
Mechanism:	Ligand binding
Method of detection:	PET
Source of signal:	^{11}C
Activation:	No
***In vitro* studies:**	Yes
Rodent studies:	Yes
Other non-primate mammal studies:	No
Non-human primate studies:	Yes
Human studies:	No



Click on the above structure for additional information in PubChem [http://pubchem.ncbi.nlm.nih.gov].

Background

[PubMed]

The serotonin neurotransmitter is considered to play an important role in a variety of brain functions such as appetite, sleep, and mood. Neuropsychiatric disorders, including major depression, schizophrenia, and Alzheimer's and Parkinson's diseases (1-3), involve a dysfunction of the brain's serotonin system. The serotonergic neurons – present in wide areas of the brain, including the hypothalamus, thalamus, and cerebral cortex – bear a protein called "serotonin transporter" (SERT) (4).

The SERT, located on the cell bodies and terminals of 5-hydroxytryptamine (5-HT) neurons, is a specific marker for the number and integrity of presynaptic terminals of serotonin-producing neurons. The SERT regulates neurotransmission by removing released serotonin from the extracellular space back into the presynaptic neuron. Commonly prescribed antidepressants are selective sero-

tonin reuptake inhibitors (SSRIs), and their effect is obtained through interaction with (and inhibition of) the SERT (5). For that reason, *in vivo* imaging of the regional brain distribution of the SERT is an important tool in the treatment of neuropsychiatric disorders.

A variety of *in vivo* radioligands for positron emission tomography (PET) have been evaluated for imaging the SERT. [^{11}C]McN5652 was the first successful and widely used agent (6, 7), but it does have some limitations because of its slow brain kinetics and low to nonspecific binding ratios in humans. It is adequate for regions with high SERT density but often provides insufficient signal-to-noise differentials for imaging brain regions with intermediate to low SERT densities (e.g., limbic and neocortical regions).

Over recent years, new PET radioligands have been synthesized and evaluated as SERT imaging agents. Among them are ^{11}C-labeled *N*,*N*-dimethyl-2-(2-amino-4-cyanophenylthio)benzylamine ([^{11}C]DASB [http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=micad.chapter.DASB11C]), 2-(2-(dimethylaminomethyl)phenylthio)-5-fluoromethylphenylamine ([^{11}C]AFM [http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=micad.chapter.AFM11C]), 5-bromo-2-[2-(dimethylaminomethylphenylthio)]phenylamine ([^{11}C]DAPA), 2-[2-(dimethylaminomethylphenylthio)]-5-iodophenylamine ([^{11}C]ADAM), and *N,N*-dimethyl-2-(2´-amino-4´-hydroxymethylphenylthio)benzylamine ([^{11}C]HOMADAM [http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=micad.chapter.HOMADAM]), which are based on a diaryl sulfide motif (4). [^{11}C]2-(2-((Dimethylamino)methyl)phenylthio)-5-(2-fluoroethyl)phenylamine ([^{11}C]AFE) has shown a high binding affinity and good selectivity for the SERT and displays signal-to-noise ratios that may enable more reliable mapping of brain regions with low SERT density.

Synthesis

[PubMed]

[^{11}C]AFE can be prepared from its monomethylamino precursor 5-(2-fluoroethyl)-2-(2-((methylamino)methyl)-phenylthio)phenylamine by reaction with either [^{11}C]methyl triflate ([^{11}C]MeOTf) (8) or [^{11}C]MeI, as described by Zhu et al. (9).

In the first method (with [^{11}C]MeOTf), the precursor is dissolved in acetone and [^{11}C]MeOTf is bubbled through the solution at room temperature. Once maximum activity is reached, the mixture is heated (70 °C for 5 min in a water bath) and purified by high-performance liquid chromatography (HPLC; 40% acetonitrile–60% 0.1 ammonium acetate, pH 6.8). The product is then eluted (~12 min), diluted in 100 ml of H_2O, loaded on a SepPak, and then eluted with ethanol. The ethanol solution is then mixed with 0.9% sterile saline and filtered through a 0.22 μm membrane to obtain the final product, [^{11}C]AFE.

In the second method, [^{11}C]AFE is prepared via reaction of the precursor with [^{11}C]MeI (trapped at –10 °C). The reaction is performed at 80 °C for 5 min.

The reported radiochemical purity of [^{11}C]AFE produced by the first method is >95% (determined by HPLC). The reported radiochemical yields at the end of the synthesis are 32 ± 17% (decay-corrected, based on [^{11}C]MeOTf; n = 6) in the first method (8) and 26 ± 14% (decay-corrected, based

on [^{11}C]MeI; *n* = 4) in the second method (9). The specific activities of the radiotracer produced are 61,790 ± 32,190 GBq/mmol (1,670 ± 864 Ci/mmol) and 32,079 ± 16,502 GBq/mmol (867 ± 446 Ci/mmol) for the first (8) and second methods (9), respectively.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

The affinities of [^{11}C]AFE for the monoamine transporters SERT, dopamine transporter (DAT), and norepinephrine transporter (NET) were determined *in vitro* by Zhu et al. (9). Experiments were performed with cloned human receptors transfected on HEK-293 cells and the radioligands [^{3}H] paroxetine (for SERT), [^{3}H]nisoxetine (for NET), and [^{3}H]GBR2935 (for DAT). Experiments were performed according to a previously published procedure (10).

[^{11}C]AFE displayed a high affinity for SERT (K_i = 1.80 ± 0.07 nM), but much lower affinities for NET (K_i = 946.2 ± 222.5 nM) and DAT ($K_i > 10^4$ nM). Additional assays showed that [^{11}C]AFE displayed virtually no affinity for benzodiazepine, opioid (μ, σ, and κ) receptors, or for serotonin and dopamine receptors such as 5-HT_{1A}, 5-HT_{2a}, 5-HT_{2c}, 5-HT_3, 5-HT_6, 5-HT_7, and D_1-D_5.

Animal Studies

Rodents

[PubMed]

Ex vivo biodistribution studies were performed on Sprague-Dawley rats by Zhu et al. (9). The experimental procedure involved injecting 3.7 MBq (100 μCi) of [^{11}C]AFE per animal (into the tail vein) and measuring the uptake of the radiotracer at various time points after injection of the radiotracer.

Results showed an overall rapid uptake of [^{11}C]AFE into the brain. At 10 min post injection, the measured uptake was 0.8% of the injected dose (ID)/g of tissue. After clearance of the nonspecific binding, [^{11}C]AFE showed an uptake pattern consistent with the distribution of SERT in rat brain. The highest levels were found in the hypothalamus, thalamus, frontal cortex, and striatum. The reported specific/nonspecific binding ratios (i.e., ratio of % ID/g in the region of interest to that in the cerebellum) were approximately 5.5 for the hypothalamus and 4.1 for the thalamus at 60 after injection of the tracer.

When pretreated with either cold AFE (2 mg/kg of tissue, given at 10-15 before injection of [^{11}C]AFE) or citalopram (an SSRI), 44-62% of the specific binding in the hypothalamus was found to be displaced at 45 min after injection of the tracer. In contrast, pretreatment with nisoxetine (a selective norepinephrine reuptake inhibitor) did not lead to any significant change with respect to [^{11}C]AFE-specific binding in SERT-rich regions. Those results indicated that [^{11}C]AFE had a high binding selectivity for the SERT.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

PET brain imaging studies of 3 male baboons (12 to 32 kg) were performed by Zhu et al. (9) for time periods ranging from 0 to 120 min after administration of [^{11}C]AFE (injected dose: approximately 185 MBq (5 mCi); specific activity at time of injection: ~26.7 ± 9.1 GBq/mol (990 ± 338 Ci/mmol); injected mass: 1.66 ± 0.47 μg). The highest levels of the tracer were found in regions of high SERT densities (e.g., thalamus, midbrain, and striatum), and the lowest levels were found in the cerebellum. [^{11}C]2-[2-(Dimethylaminomethylphenylthio)]-5-fluorophenylamine ([^{11}C]AFA) exhibited rapid uptake kinetics, with activity peaks between 15 and 40 min post injection.

When the baboons were pretreated with 2 mg/kg (4.8 ± 0.5 mCi) of citalopram (an SSRI) 20 min before injection of [^{11}C]AFE, the radiotracer uptakes in the midbrain, thalamus, striatum, hippocampus, and cortex were reduced to the level of the cerebellum, showing a significant reduction of the specific binding of [^{11}C]AFE in all SERT-containing brain regions. A kinetic analysis done by the authors of the study (9) showed that the regional equilibrium specific-to-nonspecific partition coefficient of [^{11}C]AFE was similar to that obtained for the other imaging agent, [^{11}C]AFA (with peak uptake occurring between 15 and 40 min after injection of the radiotracer), but lower than those obtained for [^{11}C]DASB [http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=micad.chapter.DASB11C] (e.g., mid-brain: 0.83 ± 0.17, 0.95 ± 0.07, and 1.68 ± 0.23 for [^{11}C]AFE, [^{11}C]AFA, and [^{11}C]DASB respectively). In comparison, the regional equilibrium specific-to-nonspecific partition coefficients for [^{11}C]AFM and [^{11}C]McN5652 that were reported previously in the literature (11) were 0.94 ± 0.18 ([^{11}C]McN5652) and 2.14 ± 0.16 ([^{11}C]AFM), respectively.

Human Studies

[PubMed]

No publication is currently available.

References

1. Owens MJ, Nemeroff CB. The serotonin transporter and depression. Depress Anxiety 8:5–12; 1998. (PubMed)
2. Palmer AM, Francis PT, Benton JS, Sims NR, Mann DM, Neary D, Snowden JS, Bowen DM. Presynaptic serotonergic dysfunction in patients with Alzheimer's disease. J Neurochem 48(1):8–15; 1987. (PubMed)
3. Roth BL, Xia Z. Molecular and cellular mechanisms for the polarized sorting of serotonin receptors: relevance for genesis and treatment of psychosis. Crit Rev Neurobiol 16(4):229–236; 2004. (PubMed)
4. Laakso A, Hietala J. PET studies of brain monoamine transporters. Curr Pharm Des 6(16):1611–1623; 2000. (PubMed)
5. White KJ, Walline CC, Barker EL. Serotonin transporters: implications for antidepressant drug development. Aaps J 7(2):E421–E433; 2005. (PubMed)

6. Ichimiya T, Suhara T, Sudo Y, Okubo Y, Nakayama K, Nankai M, Inoue M, Yasuno F, Takano A, Maeda J, et al. Serotonin transporter binding in patients with mood disorders: a PET study with [11C](+)McN5652. Biol Psychiatry 51(9):715–722; 2002. (PubMed)
7. Suehiro M, Scheffel U, Ravert HT, Dannals RF, Wagner HN. [11C](+)McN5652 as a radiotracer for imaging serotonin uptake sites with PET. Life Sci 53(11):883–892; 1993. (PubMed)
8. Jewett DM. A simple synthesis of [11C]methyl triflate. Int J Rad Appl Instrum [A] 43(11):1383–1385; 1992. (PubMed)
9. Zhu Z, Guo N, Narendran R, Erritzoe D, Ekelund J, Hwang DR, Bae SA, Laruelle M, Huang Y. The new PET imaging agent [11C]AFE is a selective serotonin transporter ligand with fast brain uptake kinetics. Nucl Med Biol 31(8):983–994; 2004. (PubMed)
10. Huang Y, Hwang DR, Zhu Z, Bae SA, Guo N, Sudo Y, Kegeles LS, Laruelle M. Synthesis and pharmacological characterization of a new PET ligand for the serotonin transporter: [11C]5-bromo-2-[2-(dimethylaminomethylphenylsulfanyl)]phenylamine ([11C]DAPA). Nucl Med Biol 29(7):741–751; 2002. (PubMed)
11. Huang Y, Hwang DR, Narendran R, Sudo Y, Chatterjee R, Bae SA, Mawlawi O, Kegeles LS, Wilson AA, Kung HF, et al. Comparative evaluation in nonhuman primates of five PET radiotracers for imaging the serotonin transporters: [11C]McN 5652, [11C]ADAM, [11C]DASB, [11C]DAPA, and [11C]AFM. J Cereb Blood Flow Metab 22(11):1377–1398; 2002. (PubMed)